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10/538,716	06/10/2005	Toshiya Fujisato	AKA-0286	6913
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MILLEN, WHITE, ZELANO & BRANIGAN, P.C.			EXAMINER	
2200 CLARENDON BLVD.			TON, THAIAN N	
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/538,716	Applicant(s) FUJISATO ET AL.
	Examiner Thaian N. Ton	Art Unit 1632

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --
Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
 - If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
 - Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED. (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(o).

Status

- 1) Responsive to communication(s) filed on 10 November 2008.
- 2a) This action is FINAL. 2b) This action is non-final.
- 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) Claim(s) 5 and 7-12 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) Claim(s) _____ is/are allowed.
- 6) Claim(s) 5, 7-12 is/are rejected.
- 7) Claim(s) _____ is/are objected to.
- 8) Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) The specification is objected to by the Examiner.
- 10) The drawing(s) filed on _____ is/are: a) accepted or b) objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) All b) Some * c) None of:
 1. Certified copies of the priority documents have been received.
 2. Certified copies of the priority documents have been received in Application No. _____.
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date: _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO/US/06)
Paper No(s)/Mail Date: _____ | 6) <input type="checkbox"/> Other: _____ |

DETAILED ACTION

The Examiner of Record is now **Thaian N. Ton** of Art Unit 1632.

Applicants' Amendment and Response, filed 11/10/08, has been entered and considered. Claim 10 is amended; claim 12 is newly added; claim 4 is cancelled; claims 5, 7-12 are pending and under current examination.

Claim Rejections - 35 USC § 112

The prior rejection of claims 4-5, 7-9 and 10-11 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement, for new matter, is withdrawn in view of Applicants' amendment to the claims which now recites that the cellular components are removed from said tissue. The specification on p. 12, ¶23 discusses irradiation with microwave to remove cells, and ¶24 discusses that the tissue was "decellularized" by irradiation with microwave in conjunction with treatment of the detergent solution alone.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 12 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This is a new matter rejection. 37 CFR 1.118 (a) states that "No amendment shall introduce new matter into the disclosure of an application after the filing date of the application". This is a new ground of rejection, necessitated by Applicants' amendment to the claims.

Applicants have now added claim 12, which is directed to a method of decellularizing native tissue of mammalian origin comprising irradiating with microwaves tissue immersed in a treating solution containing a detergent, while maintaining the temperature of the tissue in the range between 0-40°C, wherein complete decellularization of the tissue is effected.

Applicants point to page 12, ¶24 for support for this claim amendment. The Examiner notes that paragraphs 23-24 discuss the methods of the invention, and state that the methods result in decellularization, and that the "porcine pulmonary valve leaflet was decellularized even in deep interior portions by irradiation with microwave in conjunction with the treatment of detergent solution." See p. 12, ¶24. Thus, this portion of the specification, although teaching that the tissue becomes decellularized, or that cellular components are removed, the as-filed disclosures does not provide support for complete decellularization of the tissue. The specification teaches that methods of the art do not provide complete decellularization (p. 4) but does not teach that the methods of the claimed invention would result in complete decellularization of the tissue. Accordingly, the limitation of "complete decellularization" is not supported by the as-filed disclosure.

To the extent that the methods are not described in the instant disclosure, claim 12 is also rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention, since a disclosure cannot teach one to make or use something that has not been described.

MPEP §2163.06 notes:

If new matter is added to the claims, the examiner should reject the claims under 35 U.S.C. 112, first paragraph - written description requirement. In re Rasmussen, 650 F.2d 1212, 211 USPQ 323 (CCPA 1981).

MPEP §2163.02 teaches that:

Whenever the issue arises, the fundamental factual inquiry is whether a claim defines an invention that is clearly conveyed to those skilled in the art at the time the application was filed...If a claim is amended to include subject matter, limitations, or terminology not present in the application as filed, involving a departure from, addition to, or deletion from the disclosure of the application as filed, the examiner should conclude that the claimed subject matter is not described in that application.

MPEP §2163.06 further notes:

When an amendment is filed in reply to an objection or rejection based on 35 U.S.C. 112, first paragraph, a study of the entire application is often necessary to determine whether or not "new matter" is involved. Applicant should therefore specifically point out the support for any amendments made to the disclosure. (Emphasis added).

Claim Rejections - 35 USC § 102

The prior rejection of claims 5, 7-9 and 10 under 35 U.S.C. 102(b) as being anticipated by Login et al (US 4994237, 1991) is withdrawn in view of Applicants' amendment to the claims which now require that the microwave is at a frequency of 2450 MHz for a net period of time of at least 1 hour.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary.

Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 5, 7-11 are rejected under 35 U.S.C. 103(a) as being unpatentable over Login et al (US 4994237, 1991) in further in view of Giberson et al (US 6875583, 2005) and Boon et al (EP0362438A1, 1990). This rejection is maintained for reasons of record advanced in the prior Office action, mailed 5/9/08.

Applicants' Arguments. Applicants argue that Login disclose a process of employing microwave irradiation along with a physiological salt solution, and that they use an osmotically balanced solution (OBS), whose purpose is to prevent the loss of cellular constituents due to diffusion, and that their techniques deal with "tissue fixing" and not decellularization, which is the claimed invention. In particular, Applicants argue that immersion or treatment in an OBS taught by Login would not work because the tissues are immersed in the treating solution with considerable greater intensity for a net period of time to achieve complete decellularization. Applicants argue that Login never irradiates the tissue specimen in OBS with microwave energy at a dose and for a duration of time such that the temperature of the solution reaches above (35-50°C). See page 5 of the Response. Applicants argue that Giberson teach using formalin to immerse a specimen and irradiate with microwave, and formalin is well known as a fixation chemical of biological tissues for microscopic inspection, and therefore they do not remove any cellular component from the tissue. Applicants argue that Boon teaches the use of alcohol or glutaraldehyde, which is directed to fixing cells. Applicants argue that the secondary references do not remedy the deficiencies of Login, and even in combination do not suggest the present claims. See p. 6 of the Response.

Response to Arguments. Applicants are arguing limitations that are not found within the claims. In particular, the claims do not require complete decellularization, merely “decellularization” of the tissue (see claim 11). Thus, any amount of decellularization would fulfill the limitation of the claims. Additionally, Login provide guidance for a temperature range that is within the claimed range of the instant invention (35-50°C). Thus, given that Login provide guidance for immersing tissues in a solution that contains a detergent (as required by the claims), and additionally, that they teach the temperature range, and microwaving the tissue, as required by the claims, it is reasonably argued that some type/degree of decellularization would reasonably occur. The claims do not require any degree or amount of decellularization. Even if Login’s solution is meant to prevent the loss of important cellular constituents, given that their OBS contains a detergent, which is the only component in the solution required by the instant claims, it would be a necessary property of the solution to produce some amount of decellularization.

Applicants’ claims do not distinguish from the art of record, because the art of record provides the ranges of time, temperature and frequency of microwave, and requirements of the solution components (detergent). Thus, the art of record provides sufficient teachings and motivation to arrive at the claimed invention, which is “decellularization,” to any degree, of the tissue. This encompasses a single cell being decellularized in the tissue. The claims are not limited in scope to anything outside of the ranges taught by the art, and therefore, the art renders the claimed invention obvious.

Login et al teaches a method to prepare biological tissues (e.g. heart valves, veins, cartilage, ligaments) and organs for use as bioprostheses, and more particularly, it relates to a rapid method to preserve tissue samples with a solution, to irradiate samples in a microwave oven (*Note: standard microwave oven operates at 2.45 GHz see Boon et al EP0362438A1, 1990*), and to store samples in a storage medium (see Fig-1, Spec. col.1, lines 12-20. also Col. 8-10 i.e. claims). The cited art

further teaches that microwave irradiation in conjunction with a physiologic salt solution or a dilute aldehyde solution, leads to a degree of preservation such that tissue flexibility is promoted and collagen cross-linking is minimized. The cited art further teaches that the object of the present invention is to preserve biologic tissue for implantation into animals or humans such that the bioprosthesis will function physiologically (i.e. resist mechanical failure under physiologic conditions). In order to achieve this goal, microwave energy is used to irradiate the tissue (see Spec. col.5, lines 60-). The cited art further teaches that the tissue is immersed in an osmotically balanced solution (OBS, see table-1) and then irradiated in a microwave oven until the OBS reaches a temperature within the range of 35°C to 50°C. The cited art further teaches that after the microwave irradiation, the tissue is transferred and stored in a cold sterile saline solution (see Spec. col. 3, lines 53-68).

The cited art further teaches that the broadest aspects of the invention involve removing the tissue from its blood supply, immersing the tissue in an osmotically balanced solution (OBS) initially at room temperature (approximately 20°C), irradiating the immersed tissue with microwave energy at a sufficient dose and for a sufficient time such that the temperature of the solution is within the range of 35°C. to 50°C, and storing the tissue in a sterile OBS until it is implanted in a patient (see spec col.4, lines 35-45).

The cited art further teaches a comparison study using pig heart valves, wherein the valve leaflets were rinsed in standard electrolyte solution and fixed using three different treatment methods: (a) immersion in a 0.6% glutaraldehyde solution for 24 hours at 25°C. (b) immersion in an aldehyde OBS at 22°C and exposure to microwave irradiation for 11 seconds to reach a final solution temperature of 47°C and (c) immersion in an aldehyde OBS at 22°C. wherein irradiation exposure time was limited to 8 seconds at which time the solution reached a final temperature of 40°C. The cited art teaches that the microwave

treated samples were removed from the warm solution within thirty seconds and were stored in 0.9% saline at 4°C with 0.02% sodium azide (see col.6, line 20-).

In addition, if the prior art structure is capable of performing the intended use, then it meets the claim. In a claim drawn to a process of making, the intended use must result in a manipulative difference as compared to the prior art. *See In re Casey, 152 USPQ 235 (CCPA 1967) and In re Otto, 136 USPQ 458, 459 (CCPA 1963)*. In the instant case Login et al clearly teaches that the immersed tissue are irradiated with microwave energy at a sufficient dose and for a sufficient time such that the temperature of the solution is within the range of 35°C to 50°C, which would lead to decellularization as claimed (see spec col.4, lines 35-45). Thus given the broadest reasonable interpretation the cited art clearly provides guidance for the invention as claimed.

Even though Login et al teaches a method to preparing tissue using microwave treatment while maintaining the maintaining the temperature between 0°C to 40°C, the cited art does not teach that the temperature is maintained via heat-exchange contact with a coolant liquid received in a microwave-transmitting vessel, and wherein said tissue is irradiated with microwaves in a microwave oven (at 2450 MHz) from 1 hour to 1 week, while circulating said coolant liquid through a cooling apparatus provided externally of the microwave oven.

Giberson et al (US 6875583, 2005) teaches microwave-treatment of fresh tissue, comprising immersing the tissue in a solution comprising a detergent and heating the immersed tissue using a microwave at a temperature of 4°C to 40°C by pumping the fixation solution through a cooling apparatus which is outside of the microwave oven for 1 hour. Giberson further teaches that the thickest tissues require approximately 60 min of microwave treatment (see fig-1, col. 5, lines 62-67, col. 10-12).

Boon et al (EP0362438A, 1990) teaches microwave treatment of xenogeneic cartilage transplants using standard microwave device that operates at 2.45 GHz.

Thus it would have been obvious to one ordinary skilled in the art at the time the instant invention was made to modify the invention of Login et al with Giberson et al by incorporating a heat exchange device that can maintain temperature in the range of 0-40°C using a standard microwave device that operates at 2.45 GHz as taught by Boon et al. One would have been motivated to do so to control tissue overheating during microwave treatment. One would have a reasonable expectation of success, since use of microwave irradiation (*using standard microwave ovens that operate at 2.45 GHz*) to treat tissue sample of choice has been routine in the art at time the instant invention was made. Thus the invention as claimed is *prima facie* obvious in view of cited prior art of record.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Thaian N. Ton whose telephone number is (571)272-0736. The examiner can normally be reached on 9-5:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on 571-272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-21 7-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Thaian N. Ton/
Primary Examiner, Art Unit 1632